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National Children's Study

Health Disparities / Environmental Justice Workgroup

Traffic Exposure and Asthma Onset in Children

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I. Proposed Hypothesis:

Asthma frequency and asthma morbidity are elevated among urban socioeconomically disadvantaged populations in the United States, compared to urban populations that are more socioeconomically advantaged. Asthma rates are not elevated in all non-urban socioeconomically disadvantaged United States populations.

1.In-utero and early childhood exposure to diesel exhaust is associated with alteration of immune function, as measured by

a. deviation of T-cell responses toward expression of pro-inflammatory cytokine by 2 years of age
b. increased esosinophilia and allergy as measured by IgE level and skin test sensitization as early as 2 years of age

2. In-utero and early childhood exposure to diesel exhaust is associated with subsequent onset of asthma with allergy. The primary outcome associated with this hypothesis is asthma development (onset).
3. Once allergy and asthma have developed, childhood exposure to diesel exhaust is associated with exacerbation of asthma symptoms
4. The excess of asthma among socioeconomically disadvantaged group in urban environments can be explained, in part by traffic patterns and differential exposure to diesel exhaust.
5. Environment-by-environment interactions exist, making socioeconomically **disadvantaged** urban populations more susceptible to the effects of diesel exhaust than more advantaged urban populations.

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IV. Public Health Significance

Asthma has been a rapidly growing public health problem approaching epidemic proportions in some parts of the United States. The prevalence of asthma nationwide increased 59% between

1982 and 1996 (NCHS, 2000). The burden of asthma is borne disproportionately by African-Americans and persons under the age of 18. In 1996 the prevalence of asthma among African-Americans was 69.6 per 1000, compared to 53.5 per 1000 for whites, and 55.2 for the general population. Among the age groups asthma prevalence is highest in those under age 18, 62 per 1000. The greatest increase in the prevalence and severity of asthma has been among children and young adults living in poor inner-city neighborhoods (Eggleston et al., 1999). Asthma is at epidemic proportions in urban, minority, and low-income populations, a health burden that epitomizes the health disparities between minority and non-minority, low-income and middle to high income.

Diesel exhaust is a particular concern in many low-income minority urban neighborhoods that bear a disproportionate burden of diesel sources. Low-income and minority individuals are more likely to live close to sources of diesel emissions: highways, and land uses that house or attract diesel buses and trucks, including depots, trash transfer stations, and rail yards. Additionally, urban areas have higher ambient concentrations of diesel exhaust particles than do suburban or rural areas.

Although ambient air quality has decreased nationwide since 1970, emissions from diesel vehicles have not. Total diesel truck sales and diesel truck sales as a percentage of total truck sales have increased significantly during that same time period. While overall emissions of PM_{10} from diesel vehicles have decreased during that time period, primarily as a result of lowered sulfur content of fuel, the impact on emissions of fine particulates ($PM_{2.5}$) and emissions of ultrafine particulates is not as clear.

V. Justification for a large, prospective, longitudinal study

The complex etiology of asthma necessitates a large cohort in order to isolate potential impacts of diesel. Analyzing factors associated with onset of asthma is best done prospectively. Additionally, a prospective methodology enables a more accurate exposure assessment and avoids selection bias. A large cohort is also necessary to ensure enough variability in exposure, particularly within similar racial / ethnic groups. For example, a large cohort would enable analyzing whether, among African-Americans from a variety of urban and rural backgrounds, traffic patterns explain differences in wheeze or asthma development. Moreover, a cohort of 100,000 would increase the potential to evaluate whether other environmental factors (e.g. allergen exposure, stress) interact with local traffic/diesal exposure to explain health disparities in the risk of wheeze in infancy, asthma development or asthma morbidity.

VI. Scientific Merit

While many types of ambient air pollution have decreased in the past 20-30 years, mobile source pollution and in particular diesel exhaust have remained constant or possibly increased. Urban areas are home to both the highest concentration of diesel sources as well as the most rapid increase in asthma rates and morbidity. Furthermore, the racial/ethnic and socioeconomic groups that have the greatest prevalence of asthma also have the highest exposures to diesel exhaust.

A growing body of experimental and clinical evidence supports an irritant and immunologic impact of diesel exhaust particles. through enhancement of IgE production, adjuvant effect, upregulation of mast cell recruitment and histamine release, increase in plasma cell IgE production, increase in neutrophil and eosinophil recruitment and mediator release, increase in epithelial cell H_1 receptor expression and synthesis of IL-6, IL 8 and GM-CSF, increase in T-cell recruitment and TH2 type cytokine expression, and increase in macrophage recruitment and mediator release. These effects are consistently proinflammatory and allergy enhancing (Salvi et al., 1999; Diaz-Sanchez, 1997; Nel et al., 1998; Peterson et al, 1996; Ohta et al., 1999; Abe et al. 2000).

Diesel exhaust particles may act to potentiate the allergenicity of some proteins. One study has shown diesel particles act as an adjuvant to ragweed allergen (Diaz-Sanchez (1997a)).

Thus far the evidence supports a plausible mechanism for exacerbation of pre-existing asthma. However, to date little evidence exists regarding the potential for the immunologic effects of DEP to affect onset of asthma. One study demonstrated DEP induced sensitization to a neoantigen among 9 of 15 subjects. (Diaz-Sanchez D., 1999) This hypothesis focuses on the potential of diesel exhaust particles to contribute to asthma onset via its immune altering actions.

Biological Mechanisms: Clinical and Experimental Evidence

Emerging experimental evidence of irritant and/or immunologic effects of diesel exhaust on the respiratory system may have special relevance in inner city neighborhoods. Diesel particles have been shown to enhance in vivo and in vitro expression of IgE, the immunoglobulin characteristic of allergic response. In vitro studies using human B-cells have shown that the polyaromatic hydrocarbons (PAHs) extracted from diesel exhaust enhanced IgE production by these cells (Takenaka et al., 1995). One proposed mechanism is via stimulation of the aromatic hydrocarbon (Ah) receptor complex. Another hypothetical mechanism is that diesel particles themselves act as adjuvants by adsorbing antigens and prolonging their retention in the lungs (Diaz-Sanchez et al., 1994), or that the PAH pyrene, commonly found in diesel exhaust, acts as an adjuvant (Suzuki et al., 1993). Other studies have shown that DEP induces oxidative stress (Li et al., 2000).

In vivo experiments also support the hypothesis that DEP exposure is associated with IgE production and enhances the immune response. Intraperitoneal injection in vivo to mice of DEP has been shown to increase IgE to response to other antigens (Takafuji et al., 1987). These responses however have been produced also with other types of particles suggesting that the composition may not play a critical role.

Experimental studies indicate that DEPs can interact with a vast array of respiratory cells and proteins. Effects of exposure include, upregulation of mast cell recruitment and histamine release, increase in plasma cell IgE production, increase in neutrophil and eosinophil recruitment and mediator release, increase in epithelial cell H_1 receptor expression and synthesis of IL-6, IL 8 and GM-CSF, increase in T-cell recruitment and TH2 type cytokine expression, and increase in macrophage recruitment and mediator release. These effects are consistently proinflammatory and allergy enhancing (Salvi et al., 1999; Diaz-Sanchez, 1997b; Nel et al., 1998; Peterson et al, 1996; Ohta et al., 1999; Abe et al. 2000).

In one experimental study either saline alone or 300 micrograms of diesel exhaust particles plus saline were sprayed into the nostrils of human subjects. The DEP spray was found to induce significant increases in IgE production, which peaked 4 days after the nasal challenge and returned to normal by the seventh day (Diaz-Sanchez et al, 1997b). The authors noted that although 300 μg of DEP was equivalent to total exposure over one to three average days in Los Angeles, "this level of exposure can occur in certain non-occupational settings, such as sitting at a busy bus stop or in an express highway tunnel." An earlier study showed that human bronchial epithelial cells showed decreased ciliary beat frequency following exposure to DEP extract, and increased release of inflammatory mediators (Bayram et al., 1998). Subsequently it was shown that DEPs induce time- and dose-dependent damage to the membranes of human airway epithelial cells cultivated in vitro (Boland et al., 1999). Another study in healthy human subjects showed increased recruitment of neutrophil and alveolar macrophages into the airways along with suppressed macrophage functions after exposure to diesel exhaust (Rudell et al., 1999).

DEP surfaces may also act as a site for the concentration of airborne allergens such as pollen grains and roach and mite proteins (Knox et al., 1997). The small particle size that allows DEP to penetrate deep into the lower respiratory airways and the ability to act as a carrier for toxic organic chemicals, and allergens, provides additional insights as to the possible mechanism of action.

Epidemiological Evidence

The results of these studies show biologically plausible mechanisms for an association between human exposure to diesel exhaust particles and the development of asthma or the onset of inflammatory response. Recent epidemiological studies have also explored this association. A few researchers have conducted cross-sectional studies examining the relationship between children's acute and chronic experiences of respiratory distress and their proximity to motor vehicles from highways. Wjst et al (1993). showed a small but significant decrease in peak expiratory flow (PEF) among 10-year old children in school districts in Munich with higher flow of car traffic, as well as increased self-reports of respiratory symptoms. Other analyses found that decreases in lung function and parental report of chronic respiratory symptoms were associated with truck traffic density and with concentration of black smoke measured in schools in the Netherlands (Van Vliet et al., 1997; Brunekreef et al., 1997). One case-control study found a linear trend between hospital admissions for asthma and traffic flow (Edwards et al., 1994), while another found a positive association between wheezing and symptoms of allergic rhinitis and self-reported frequency of truck traffic (Duhme et al., 1996).

While these epidemiological studies suggest an association between traffic density and asthma incidence and morbidity, they have all been limited by their short duration and small sample sizes. A large prospective study will best advance our understanding of a possible association between exposure to traffic pattern, and diesel exhaust in particular, and development and exacerbation of childhood asthma.

VII. Potential for innovative research

The proposed hypothesis offers the potential to employ and refine innovative measures of traffic patterns, including computer models and traffic counting equipment. Additionally, by increasing our understanding of children's exposures to traffic patterns and the potential contribution of diesel exhaust to childhood asthma, this research will facilitate more efficient allocation of public resources to those environmental factors posing the most significant asthma burden on children.

VIII. Feasibility

Exposure measure: Exposure to 1) traffic patterns, including diesel traffic, and 2) diesel exhaust. There are several possible measures. Traffic models can be used to assess proximity of childrens' homes to major diesel sources such as highways and bus depots and assign each study participant an exposure index. A more accurate method would be needed to separate diesel emissions from traffic density generally. One option is to refine the traffic model by conducting an traffic count to assess relative density of heavy-duty (diesel-fueled) vehicles to other vehicles on major roads near study participant's homes. More detailed traffic counts in a subset of the study population would refine traffic models, in order to improve estimates of diesel-fueled vehicles versus other vehicle. This detailed monitoring would enable the separation of estimates of exposure to diesel exhaust from that of other traffic-related pollutants. The advantage of estimating exposure to varying traffic patterns using traffic models is that it minimizes the burden on the study participant.

Studies to-date have suggested that black carbon, also known as elemental carbon (EC), provides a useful surrogate for diesel exhaust particles (DEP). Exposure to diesel exhaust is best estimated through monitoring of black carbon in the home, or personal exposure monitoring of pregnant women. In-home sampling of a subset of participants will provide a more accurate measure of exposure to diesel exhaust. Reliable home-based and personal sampling methods for exposure to black carbon have been developed and employed, in particular by the Center for Children's Environmental Health at Columbia's Mailman School of Public Health.

The exposure window of interest is in-utero and up to 24 months of age.

Outcome assessment:

1) In-utero and early childhood alteration of immune function, measured by:
   - deviation of T-cell responses toward expression of pro-inflammatory cytokine by 2 years of age
   - increased esosinophilia and allergy as measured by IgE level and skin test sensitization as early as 2 years of age
2) Diagnosis of asthma
3) Exacerbation of asthma, measured by:
   - number of ER visits for asthma symptoms
   - number of hospitalizations
   - relief medication use

Assessment of peripheral T-cell function may require collection and processing of blood specimens within 24-hours of collection; a sampling scheme will have to be developed for this assessment.

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